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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/147,346	03/01/1999	SHAI YARKONI	1268-073	1591

7590 12/19/2002

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EXAMINER
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ART UNIT	PAPER NUMBER
1642	

DATE MAILED: 12/19/2002

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application N .	Applicant(s)	
	09/147,346	YARKONI ET AL.	
	Examiner	Art Unit	
	Larry R. Helms	1642	

-- The MAILING DATE of this communication appears on the c ver sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *13 September 2001* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-7,9,10 and 21-29* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-7,9,10 and 21-29* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☒ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

Continued Prosecution Application

1. The request filed on 9/13/01 for a Continued Prosecution Application (CPA) under 37 CFR 1.53(d) based on parent Application No. 09/147,346 is acceptable and a CPA has been established. An action on the CPA follows.

2. Claims 1 and 2 have been amended.

Claim 29 has been added.

Claims 1-7, 9-10, 21-29 are pending and under examination.

4. The text of those sections of Title 35 U.S.C. code not included in this office action can be found in a prior Office Action.

5. The following Office Action contains some NEW GROUNDS of rejection.

Rejections Withdrawn

6. The rejection of claims 1-2, and 7 under 35 U.S.C. 102(b) as being anticipated by Nett et al (WO 90/09799, published 9/7/90, IDS paper # 10) is withdrawn in view of the amendments to the claims.

7. The rejection of claims 1, 2, and 7 under 35 U.S.C. 102(b) as being anticipated by Lombardo et al (WO 93/15751, published 8/19/93, IDS paper # 10) is withdrawn in view of the amendments to the claims.

8. The rejection of claims 1, 2, and 7 under 35 U.S.C. 102(b) as being anticipated by Rusiecki et al (IDS paper # 10) is withdrawn in view of the amendments to the claims.

9. The rejection of claims 3, 4, and 21 and 27 under 35 U.S.C. 103(a) as being unpatentable over Nett et al and further in view of Chaudhary et al (The Journal of Biological Chemistry 265:16306-16310, 1990) is withdrawn.

10. The rejection of claims 1-7, 9-10, 21-28 under 35 U.S.C. 103(a) as being unpatentable over Nett et al (WO 90/09799, published 9/7/90, IDS paper # 10), and further in view of Chaudhary et al {a} (Nature 339:394-397, 1989) and Chaudhary et al {b} (Proc. Natl. Acad. Sci. USA 84:4538-4542, 1987) is withdrawn in view of the new ground of rejection set forth below.

The following are some NEW GROUNDS of rejection

Claim Rejections - 35 USC § 103

11. Claims 1-7, 9-10, 21-28 and newly added claim 29 are rejected under 35 U.S.C. 103(a) as being unpatentable over Nett et al (U.S. Patent 5,378,688, issued 1/95), and further in view of Chaudhary et al {a} (Nature 339:394-397, 1989, PTO-892 paper #11) and Chaudhary et al {b} (Proc. Natl. Acad. Sci. USA 84:4538-4542, 1987, PTO-892, paper #11) and as evidenced by the specification.

The claims are summarized as a targeted fused chimeric toxin comprising a genetically engineered molecule fused at the cDNA level of an moiety encoding 10 amino acids of GnRH and PE wherein the PE is PE66 or PE40 wherein the toxin binds

to GnRH on adenocarcinoma cells and a method of producing such and a method comprising administering the chimeric toxin to adenocacinoma cells and a method of treating endometriosis, uterine myoma, pituitary adenoma, BPH, and polycystic breast disease with administration of the chimeric toxin. For this rejection claim 29 is interpreted to be GnRH that starts with Glu as indicated in Figure 1C (see 112 second rejection below).

Nett et al teach conjugation of gonadotropin releasing hormone (GnRH) to toxins and the GnRH is used to target cells bearing GnRH binding sites and the toxin is employed to permanently destroy cells. Nett et al also teach compositions comprising such proteins. Nett et al also teach the ten amino acids of GnRH targeted protein (see column 8 where Z can be Gly-NH2). Nett et al also teach modifications to the sequence of GnRH at positions 6 and 10 which result in higher affinity for the GnRH receptor that are 100 times more potent than the parent compound (see column 5 and 8) as well as chemically altering the GnRH molecule. Nett et al also teach production of the toxins by recombinant DNA technology and the toxin can be PE (see column 14) and administering the conjugated toxins to animals intravenously (see column 13). Nett et al also teach the GnRH/toxin conjugates can be used for treating cancer of the prostate and breast and endometriosis (see column 12, lines 58-65 and column 13, lines 20-29). Nett et al does not teach (1) a plasmid or (2) methods for ligating the oligonucleotide encoding GnRH or a toxin to produce a chimeric toxin molecule or a mutated form of PE or PE encoding for domains I and II or methods using a recombinant chimeric toxin. These deficiencies are made up in the teachings of Chaudhary et al {a} and {b}.

Chaudhary et al {a} teach a chimeric toxin comprising an immunoglobulin and a mutated form of PE consisting of domains I and II of PE in which PE is the toxic moiety (designated PE-40) and a plasmid which comprises ligating the DNA encoding for the immunoglobulin single chain upstream of the PE wherein said plasmid contains a promoter operably linked to the molecule encoding for such chimeric toxin (see Figure 1 and page 395). Chaudhary et al {a} also teach a method of producing a fusion protein toxin and methods of treating cancer.

Chaudhary et al {b} teach a recombinant fusion protein comprising transforming growth factor type alpha and PE 40 wherein PE 40 consists of domains II and III (see Figure 1 and Figure 2). Chaudhary et al {b} also teach a method of producing said fusion protein with recombinant methods and a plasmid comprising a promoter and an in vitro method of treating cancer cells (see page 4539, Assay of the Biological activity).

It would have been prima facie obvious to one of ordinary skill in the art at the time the claimed invention was made to have produced a fusion protein comprising the ten amino acids of GnRH, wherein residue(s) have been substituted in GnRH, wherein the oligonucleotide encoding for GnRH is ligated upstream to DNA encoding a mutated form of PE, wherein the fusion protein is produced by recombinant methods, wherein the plasmid encoding for such comprises a promoter, a method for producing such, compositions comprising such, and a method for administering said compositions to a patient for treatment of cancer.

One of ordinary skill in the art would have been motivated to produce the claimed invention because Nett et al teach the amino acid sequence of the GnRH (see column 5

and 8). Nett et al also teach a reason to mutate the GnRH at positions 6 and 10 to produce compounds that have higher affinity for the GnRH receptor. In addition, Nett et al teach the use of fusion protein toxins has utility in human medicine for treatment of cancer. One of ordinary skill in the art would have been motivated to produce the claimed invention because Chaudhary et al {a} teach recombinant DNA techniques have been used to produce chimeric toxin fusion proteins in E. coli. and Chaudhary et al fused the "targeting moiety" upstream of the PE toxin (See page 395 and Figure 1). One of ordinary skill in the art would also have been motivated to produce the claimed invention because Chaudhary et al {b} teach "A PE molecule which domain I has been deleted (PE40) has full ADP-ribosylation activity but has extremely low cell-killing activity because of loss of the cell-recognition domain" (see page 4538) and "We have now began to use PE40 to construct chimeric proteins in which growth factor genes or other genes have been replaced domain I to impart new and specific cell recognition properties" (see page 4538). In addition, One of ordinary skill in the art would have been motivated to produce the claimed invention by recombinant DNA techniques because Chaudhary et al {b} teach chemical conjugation of proteins to toxins result in nonspecific toxicity due to incomplete inactivation of domain I and this nonspecific toxicity is much diminished in genetically engineered chimeric PE40 toxin fusion proteins. (See page 4542). Moreover, one of ordinary skill in the art would have been motivated to produce the claimed invention because Chaudhary et al {b} teach the fusion toxin protein targeted cancer cells and resulted in cell killing activity.

Moreover, one of ordinary skill in the art would have had a reasonable expectation of success in producing the claimed invention because Chaudhary et al {b} teach the fusion protein toxin molecule comprising a deleted form of PE "has high cell-killing activity against cells "expressing the receptor and not against cells producing insufficient levels of receptor (see page 4541, discussion). Moreover, one of ordinary skill in the art would have had a reasonable expectation of success in producing the claimed invention because Chaudhary et al {a} teach they have constructed a recombinant fusion protein toxin by DNA methods in E. coli using the modified form of Pseudomonas exotoxin. (See page 396, last paragraph). One of ordinary skill in the art would also have been motivated and had a reasonable expectation of success to use the chimeric toxins in method to target adenocarcinoma cells because as evidenced by the specification it was known in the art that GnRH analogs have been demonstrated to be effective in several carcinomas of the breast, prostate, pancreas, endometrial, and ovarian (see page 2 of the specification).

Therefore, the invention as a whole was prima facie obvious to one of ordinary skill in the art at the time the invention was made, as evidenced by the references.

The response filed 9/13/01 has been carefully considured but is deemed no to be persuasive. The response states that the starting material in claim 1 are linked directly together and do not have an intermediate linking moiety and the binding sites set forth in claim 1 are different from the GnRH receptor type I and claim 29 addresses the difference in the prior art and if the starting materials of the prior art including the attached linking moieties were to be ligated through genetic engineering techniques the

resultant product would not be the same as the claimed product because the product would still have linking moieties (see pages 3-4) and the previously known compounds were not known to be useful in treatment of adenocarcinoma (see page 5). In response to these arguments, when the chimeric toxins are produced recombinantly there would not be any chemical linker there would obviously be peptide bonds linking the GnRH and the PE as described in Chaudary {a} or {b} which teach recombinant fusion proteins with no chemical linkers. Claim 29 does not distinguish over the prior art because there is no evidence that the Meth residue is residue 1 in the chimeric toxin. In fact it appears that the Glu residue is residue 1 in the GnRH protein. Also the claim has been interpreted to be that the first residue in the mature protein is Glu. Finally, it is well known in the art that ATG (which codes for Meth) would be needed as the initiation codon for the protein to be produced and it appears that the Meth is processed off of the mature protein as evidenced from Figure 1C. In addition, it also appears that the Meth is not needed because the prior art does not teach a Meth at the N-terminal of the mature protein and the GnRH is active without it. In response to the GnRH on adenocarcinoma cells, the prior art teaches the receptor on cancer carcinoma cells and it would be obvious that the product would target the receptor on any cells that contain the receptor.

Claim Rejections - 35 USC § 112

12. Claims 1-7, 9-10, 21-29 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

a. Claims 1-7, 9-10, 21-28 are indefinite for reciting "adapted to bond to GnRh" in claim 1 because the exact meaning of the phrase is not clear. Does the phrase mean there is a covalent bond formed between the toxin and the GnRH binding site or does the phrase mean the toxin binds to the binding site?

b. Claim 29 is indefinite for reciting "starts with Meth" because the exact meaning of the phrase is not clear. Does the phrase mean the cDNA encodes a Meth or does the phrase mean the GnRH protein starts with a methoinine. Figure 1C shows a Meth as ATG in the DNA, however, the Figure shows the GnRH starting with a Glu. Does the mature protein start with Meth or Glu?

Conclusion

13. No claim is allowed.

14. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Larry R. Helms, Ph.D, whose telephone number is (703) 306-5879. The examiner can normally be reached on Monday through Friday from 7:00 am to 4:30 pm, with alternate Fridays off. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Anthony Caputa, can be reached on (703) 308-3995. Any inquiry of a general nature or relating to the status of

this application or proceeding should be directed to the Group receptionist whose telephone number is (703) 308-0196.

15. Papers related to this application may be submitted to Group 1600 by facsimile transmission. Papers should be faxed to Group 1600 via the PTO Fax Center located in Crystal Mall 1. The faxing of such papers must conform with the notice published in the Official Gazette, 1096 OG 30 (November 15, 1989). The CM1 Fax Center telephone number is (703) 308-4242.

Respectfully,

Larry R. Helms Ph.D.

703-306-5879